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Current perceptive on canine cystic endometrial hyperplasia-pyometra syndrome-A review

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Abstract

Cystic endometrial hyperplasia-pyometra complex (CEH/P) is a life-threatening challenge in canine reproduction. Hormonal imbalances result in environmental and histological changes in the uterus leading to a predisposition to bacterial growth. Haematological analysis shows the total number of leucocytes is frequently elevated in cases of pyometra, although the degree is much less marked in cases of open cervix pyometra compared with closed cervix pyometra. Ovariohysterectomy is the treatment of choice for closed cervix or open cervix pyometra. If the condition is not life-threatening and the animal is enrolled in breeding programmed or particularly valuable or when the clinical situation precludes surgery, medical treatment may be considered.

Keywords: Uterus, cystic endometrial hyperplasia (CEH), hormones, canine pyometra, aglepristone

Introduction

During estrus cycle, the uterus of female dogs undergoes different morphological changes under the influence of progesterone and estrogen. Cystic endometrial hyperplasia is an abnormal response of non-castrated canine uterus under these ovarian hormones. Cystic endometrial hyperplasia and pyometra complex (CEH/P) represents a common life-threatening challenge in small animal reproduction (Pretzer, 2008; Melandri *et al.*, 2019) [37, 30]. Cystic endometrial hyperplasia (CEH)-pyometra syndrome is an acute or chronic, poly-systemic, diestrual disorder of non-castrated bitch characterized by hyperplasia of the endometrium and infiltration of inflammatory cells, which may be present in all layers of the uterus (Dow, 1957; Kennedy *et al.*, 1993) [9, 29]. However, during the animal's life, there is progressive hyperplasia, which ultimately results in the development of pathological lesions termed cystic endometrial hyperplasia several authors suggested that pyometra should be classified as CEH-pyometra complex because sub-acute endometritis later develops as CEH is the most important predisposing factor of pyometra (Sandholm *et al.*, 1975) [39]. Others suggest that CEH and pyometra should be classified separately based on differences in clinical and histopathological findings (Debosscher, *et al.*, 2001) [8]. It is common to see pyometra defined as the endometritis/cystic endometrial hyperplasia/pyometra complex (CEH/P) (Arora *et al.*, 2006) [3].

Pyometra can be defined as the pathological condition of uterus in which, there is an accumulation of purulent semisolid-liquid material inside the uterine lumen of intact bitches, generally during post progesterone dominant phase of the estrous cycle. Canine Pyometra can be classified based on the status of the cervix may be two types open-cervix and closed-cervix. Closed-cervix pyometra is a particularly more dangerous condition in comparison to open cervix because septicemia and toxemia may develop rapidly and left untreated can result in patient death. However closed-cervix pyometra needs surgical intervention to prevent its progression to sepsis and fatality in non-castrated bitch (Smith, 2006) [45].

Prevalence and History

Pyometra has consistently been shown to predominantly affect middle-aged to older-aged non castrated bitches, with mean age varying from 6.4 to 9.5 years (Dow, 1958; Ewald, 1961; Hardy 1974; Wheaton *et al.*, 1989; Sevelius *et al.*, 1990; Niskanen and Thrusfield, 1998; Egenvall *et al.*, 2001; Fukuda, 2001; Whitehead, 2008; Igna, 2011; Hagman *et al.*, 2011) [10, 14,

23, 46, 40, 34, 11, 16, 47, 26, 22]. Most researchers are given the opinion that CEH is a spontaneously occurring disease of middle-aged or old bitches (Moxon *et al.*, 2016) [32]. Jitpean *et al.*, 2014 [27] reported disease occurrence was 19% in bitches below 10 years of age and 20% in older female dogs.

High breed susceptibility is also observed in this condition include Rottweiler, Saint Bernard, Chow chow, Golden Retriever, Miniature Schnauzer, Irish Terrier, Airedale Terrier, Cavalier King Charles Spaniel, Rough Collie, and Bernese Mountain dog (Smith, 2006) [45]. However, a few breeds of intact bitches possess low risks like German Shepherd, Daschunds, and Swedish hounds. Breed susceptibility strongly represents the contribution of genotype towards an increase or decrease risk of disease (Jitpean *et al.*, 2012) [27].

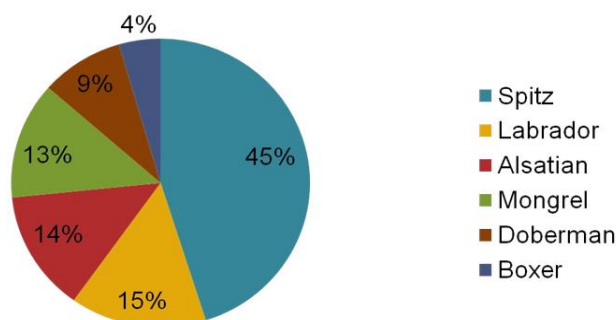


Fig 1:

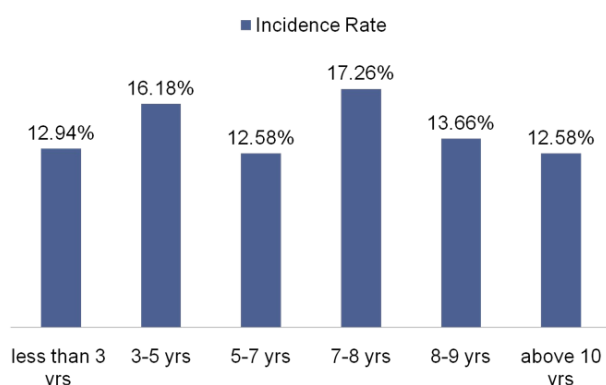


Fig 2:

Etiology

Several types of research indicated the predominant role of reproductive hormones, i.e., progesterone and estrogen as predisposing factors for pyometra in which the former being the most dominant one. Although the exact etiology of cystic endometrial hyperplasia (CEH) and pyometra is uncertain, this syndrome is probably best categorized as an infectious cause of infertility, even though the role of the endocrine environment is significant. It has been suggested that cystic endometrial hyperplasia, which precedes pyometra as a clinical disease, may cause infertility by allowing the development of mating-induced endometritis (Freeman *et al.*, 2013) [15], conception failure and embryonic resorption. The condition may be recognized by ultrasound examination of the uterus during the luteal phase. Continuing glandular hyperplasia occurs under the influence of progesterone and regresses at the end of the luteal phase. However, during the animal's life, there is progressive hyperplasia, which ultimately results in the development of pathological lesions termed cystic endometrial hyperplasia. The mean age of clinical pyometra is approximately 8 years, but it is not clear

whether there is any association with parity or characteristics of the oestrous cycle. Pyometra is, however, very clearly a disease of the luteal phase, with most bitches showing clinical signs between 5 and 80 days after the end of oestrus; progesterone is the main hormone concerned with inducing uterine glandular hyperplasia. Organisms isolated from the uterine fluid in cases of pyometra are those found as part of the normal vaginal and vulvar microflora of healthy bitches. *Escherichia coli* is the pathogen most commonly isolated from bitches with pyometra (Chen *et al.*, 2003; Hagman and Kuhn, 2002; Hagman *et al.*, 2006) [7, 20, 21].

Pathogenesis

Mainly hormonal imbalance or abnormal response to normal concentrations of oestrogens, and progesterone influence the epithelial cells of the uterus and facilitates bacterial adherence, colonization, and growth (Hagman and Kuhn, 2002) [20] that favours the occurrence of disease. During the follicular phase of estrus cycle estrogens increase the uterine cell growth and endometrial vascularization. They increase the uterine sensibility and reaction to progesterone. Progesterone results in endometrial cell proliferation and uterine glandular secretion decreased myometrial contraction and induce closure of the cervix (Borresen, 1975; Smith, 2006) [6, 45]. Factors associated with bacteria as well as their receptor expression may lead to enhance bacterial attachment to the endometrium (Gabriel *et al.*, 2016) [17].

The uterine response to the presence of microflora is largely based on innate immunity. Wijewardana *et al.*, (2015) [48] described a negative correlation between progesterone on the maturation of antigen-presenting dendritic cells which may lead to the reduction of cell-mediated immunity (CMI). Conserved pathogen-associated molecular patterns (PAMPs) synthesized by the microflora, such as lipopolysaccharide (LPS) for gram-negative bacteria, are recognized by germline-encoded pattern recognition receptors, toll-like receptors (TLRs), which induced the non-specific immune response with the recruitment of inflammatory cells, including neutrophil granulocytes (Horne *et al.*, 2008) [25]. The increased level of progesterone hormone concentrations during oestrus in the bitch may result in a less efficient nonspecific immunity, decreasing the expression of toll-like receptors (TLRs) during oestrus and early dioestrus, and allowing the embryo implantation and development (Silva *et al.*, 2012) [43]. The concomitant presence of pathogenic microflora such as *Escherichia coli* during these phases may induce the development of an infection. The bacteria adhere to the endometrium and stimulate the immune response. The expression of TLR2 and TLR4 receptors is increased (Silva *et al.*, 2010) [43], which initiate the secretion of cytokines, cyclooxygenase-2 (COX-2) and prostaglandin E2 and F2a (Silva *et al.*, 2012) [43], causing the local inflammatory response of endometrium.

Clinical Finding

If the patient is presented early, the general history is that the animal has been lethargic with a reduced appetite; increased thirst and vomiting are variable findings. Some animals may be presented later when there is a vulvar discharge, which in some cases is associated with improvement in general health. In some cases bitch remains unwell due to there is no discharge of pus from the vulva. In the other cases bitch's abdomen may become distended, and she may be thought to be pregnant, although the systemic illness is common. These cases generally end fatally, often within 14 to 21 days from

the onset of clinical signs; the cervix remains closed throughout. Death may be due to signs of pyometra include endotoxemia, septic shock, peritonitis due to rupture of the uterus, and multiorgan failure. Jitpean *et al.* (2014) [28] described peritonitis as the most common finding in pyometra which ranges 10% of total cases. Occasionally, the cervix relaxes, and there is an outpouring of pus just before death.

In a further category, there may be an intermittent opening of the cervix, with relatively good health in comparison to closed cervix after the discharge of pus and malaise during the intervening periods. Some cases of open cervix pyometra may persist for months, with a more or less continuous vulvar discharge. Body temperature may be normal or slightly elevated in cases of open cervix pyometra, whereas there is commonly observe an elevated body temperature in cases of

closed cervix pyometra. In toxemic patients the body temperature may be observed than subnormal. The character of the vulvar discharge may vary considerably. Most often, it is of a thin consistency and light chocolate brown and has a characteristic odor. In other cases, it is yellow, often blood-tinged, and varying from a watery to a creamy consistency. The vulva is generally show enlarged, and there may be discoloration or scalding of the perivulvar tissues and perineum. Increased thirst is commonly observed in advanced cases, which is due to reduced permeability for water in the distal convoluted tubule of the kidney. Renal dysfunction is probably caused by the formation of immune complexes. A small proportion of cases of pyometra develop neurological signs, particularly ear twitching.

Table 1:

Clinical signs	Open-cervix	Close-cervix
Vaginal discharge	Watery- creamy; light brown, green or yellow	rare
Temperature	normal/slightly elevated	elevated/sub-normal (toxemic bitch)
Lethargy/ depression	+	+
Vomiting	+	+
Polyuria/ polydipsia	+	+

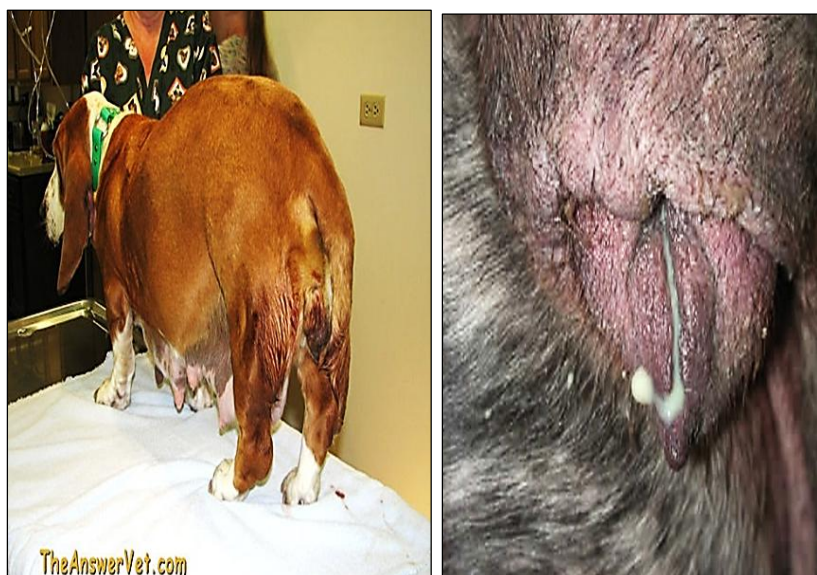


Fig 3: Diestrus bitch with purulent vaginal discharge



Fig 4: Cystic Endometrial hyperplasia

Cystic Endometrial hyperplasia

Diagnostic Features

Before abdominal palpation, animals should be allowed to urinate and defecate. But in the case of large or obese patients, abdominal palpation may be difficult. In cases of open cervix pyometra the uterine horns may be detected as thickened, often irregular, and slightly turgid structures from 1 to 3 cm in diameter. Their position within the abdomen is not generally altered from normal. Occasionally, some areas

of the uterine horns are turgid and solid on palpation whereas others, which are distended by pus, may be indistinguishable from the surrounding bowel. Care must be taken not to confuse the colon with thickened uterine horns. In cases of closed cervix pyometra, the degree of uterine distension may be greater, and there may be visible abdominal enlargement. Also palpate the distended uterus per rectum by using a finger, especially if slight backward pressure is applied to the abdominal wall and feel the enlargement of the uterus.

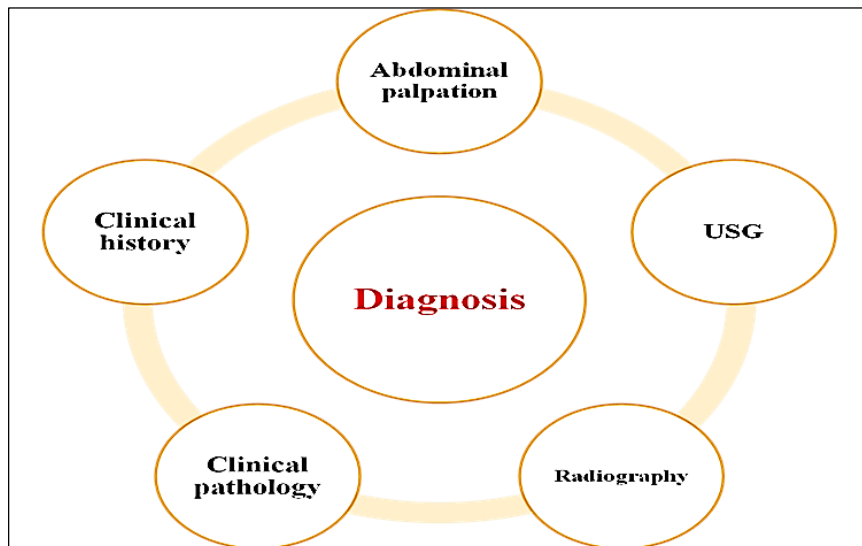


Fig 5:

Ultrasonography is an advanced diagnostic technique is particularly used for detecting the uterus that is filled with fluid. The diagnosis is most simple when the diameter of the uterus increases to larger than that of the small intestine. Ultrasonographic imaging is one of the best diagnostic tools in which uterus is observed as an enlarged and hypoechoic tubular organ containing echogenic fluid (Gupta *et al.*, 2013)

^[18], however, sometimes pus exhibits slow, whirlpool-like pattern (Bigliardi *et al.*, 2004) ^[5]. The diameter of the uterus may vary, depending on whether the cervix is open or closed. The uterine wall is usually relatively hypoechoic and is increased in thickness. The uterine lumen is usually grossly dilated with anechoic fluid, although small echogenic particles and mass lesions may be identified.



Fig 6: Uterus of bitch with pus

Uterus of Bitch with pus

Radiographic imaging of the abdominal region shows a soft-tissue-opacity mass lesion within the caudal abdomen, causing cranial displacement of the small intestine and dorsal displacement of the colon, has been used for some time to

indicate enlargement of the uterus. It should be remembered, however, that these findings are not specific for pyometra because early pregnancy has a similar radiographic appearance.

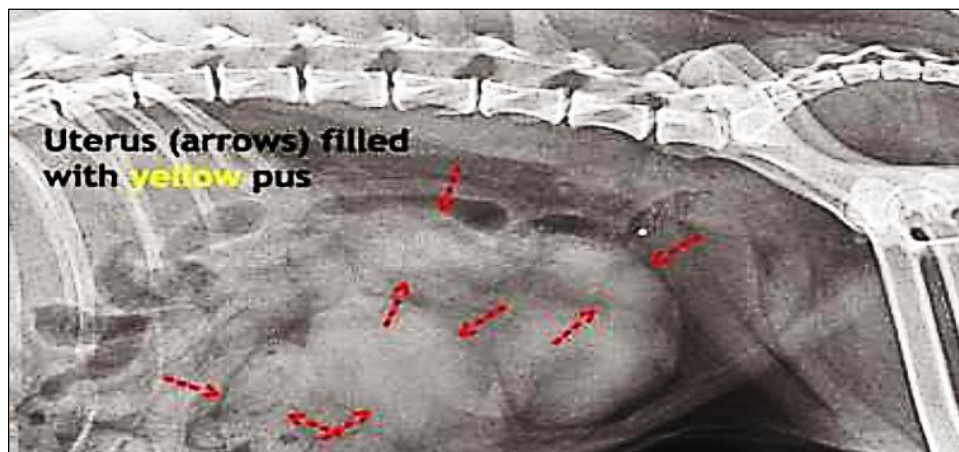


Fig 7: Distended Uterus filled with pus

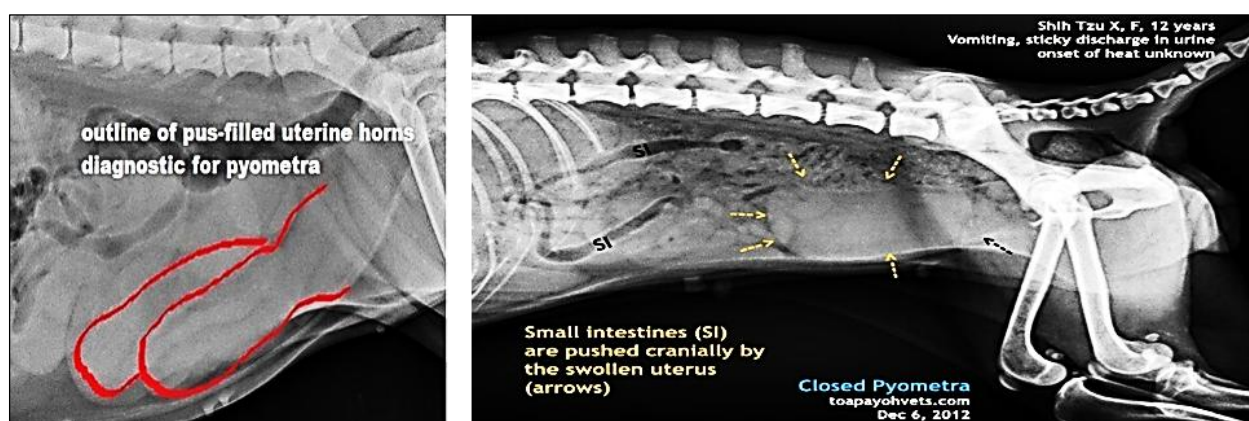


Fig 8:

Hematological analysis shows the total number of leucocytes is frequently elevated in cases of pyometra, although the degree is much less marked in cases of open cervix pyometra compared with closed cervix pyometra. However, an elevated white cell count is not always present. Haematological analysis show reduced level of haemoglobin (Hb), decreased packed cell volume (PCV), azotemia, and leucocytosis with neutrophilia as consistent findings associated with disease (Patil *et al.*, 2013) [36]. Gupta and Dhama, (2013) [18] described that reduced level of haemoglobin (Hb), packed cell volume (PCV), total erythrocyte count (TEC) and platelets along with increase level of erythrocyte sedimentation rate (ESR), total leucocytes count (TLC) and polymorphonuclear (PMN) cells indicate toxemia whereas a raised level of leucocytes, PMN cells, and declining lymphocytes point out recovery from toxemia. Therefore these changes in haematological values can be used as an aid to diagnosis as well as prognosis of canine pyometra (Mohan *et al.*, 2015) [31].

Biochemical evaluation of blood sample shows an increase in serum urea nitrogen, creatinine, ALT, AST, LP, globulin; however albumin level decreases highly significantly thus causing the enhanced ratio of globulin: albumin in pyometra

cases (Jitpean *et al.*, 2014) [28]. Destruction of tissue due to the effect of endotoxin can be attributed to elevated levels of serum urea nitrogen and creatinine. Hypoalbuminaemia and hyperglobulinaemia can be shown due to acute-phase reaction and dehydration respectively (Shah *et al.*, 2017) [41].

Treatment

Surgical Approach

Ovariohysterectomy is the treatment of choice for closed cervix or open cervix pyometra. Bitches that are presented early in the course of the disease are usually a low surgical risk in comparison to late presented cases. Lower success rates may occur when bitches are toxemic. Intravenous fluid therapy is essential required in all cases to ensure minimum renal toxic effects. Nowadays the recent technique of surgery Laparoscopic Assisted Ovariohysterectomy (LAOVH) is introduced for the treatment of canine pyometra, which is proved with lower risk sick of a surgery over conventional open method with careful case selection to improve success rate (Adamovich Rippe *et al.*, 2013; Becher-Deichsel *et al.*, 2016) [1, 17].



Fig 9:

Medical Approach

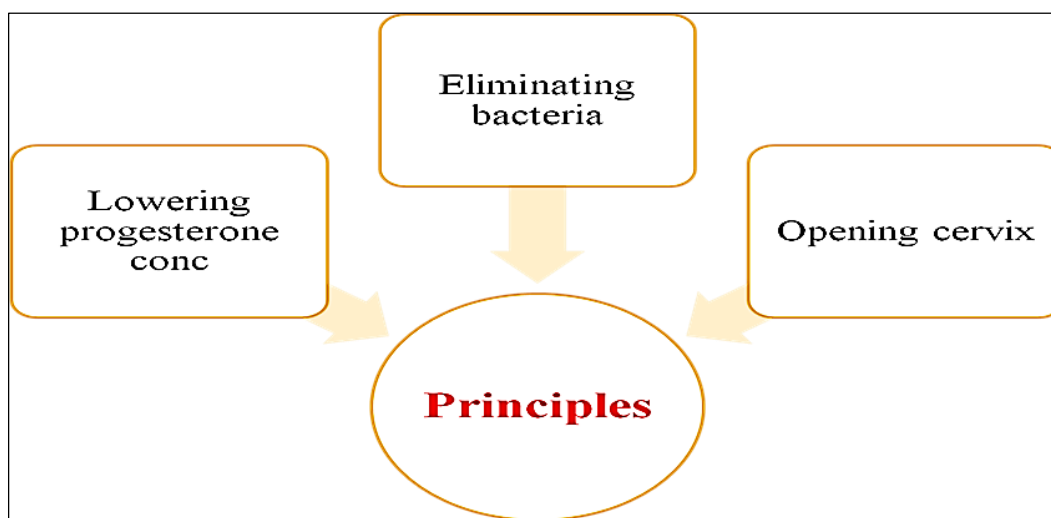


Fig 10:

If the condition is not life-threatening and the animal is enrolled in breeding programmed or particularly valuable or when the clinical situation precludes surgery, medical treatment may be considered. Medical approaches mainly include systemic and intrauterine medication of medicine. Administration of prostaglandin (PGF_{2α}) subcutaneous at the @ 150-200 µg/kg/day for more than 10 days showed 100% results (Myhre, 2016) ^[33] because PGF_{2α} causes luteolysis which leads to progesterone block (Renton *et al.*, 1993). Another protocol of treatment of pyometra with a combination of cabergoline @ 5 µg/kg PO once daily and cloprostenol @ 5µg / kg every third day subcutaneous for 10 days and potentiated sulphonamide twice a day was recorded enthusiastic results (England *et al.*, 2007) ^[13]. However, in recent times use of progesterone blockers such as mifepristone (Hoffman and Schuler, 2000) ^[24] or aglepristone (Arnold *et al.*, 2006) ^[2] are used. Progesterone blocker aglepristone with a combination of prostaglandin has proved better protocol of choice for Cystic endometrial hyperplasia-pyometra complex (CEH/P). The recent combination protocol consisted of aglepristone (@10 mg/kg SC) administration on days 1 (day of diagnosis), 2, 8, and then repeated every 7 days, repeated administration of aglepristone was ceased when the treatment end-point was achieved (normal haematological and biochemical parameter) and Cloprostenol (@1 µg/kg SC) was administered daily on days 3–5 is effective and safe, preserving subsequent fertility (Melandri *et*

al., 2019) ^[30]. Appropriate symptomatic therapies (e.g., fluid therapy, antibiotics, nonsteroidal anti-inflammatory drugs, and anti-emetic drugs) were given to patients according to their conditions. Treatment of pyometra typically includes the immediate initiation of antibiotic amoxicillin/clavulanic acid, enrofloxacin, and marbofloxacin therapy. It is likely that, in the future, more complex treatment regimes, involving combinations of these three drugs (prolactin inhibitors, prostaglandins, progesterone receptor antagonists), will prove to be even more efficacious. E Trade Name(S) Presentation Availability

Conclusion

Canine cystic endometrial hyperplasia (CEH)–pyometra syndrome is a very complex nature of the disease with one of the several reasons for this condition can be lack of complete and detailed information regarding etiopathology. The protocol of treatment of pyometra with a combination of cabergoline and cloprostenol was recorded as enthusiastic results. Progesterone receptor blocker (Aglepristone or mifepristone) alone can be effective and safe for the treatment of metritis and to induce cervical opening in closed pyometra. The recent medicinal combination of aglepristone and cloprostenol was most effective in the medical treatment for open and closed pyometra in comparison to other protocols. Nevertheless, careful selection of pyometra cases is important, and medicinal treatment is contraindicated in

bitches with hepatorenal failure or peritonitis; clinical parameters should be monitored closely throughout the treatment of bitches. It is found well established medical treatment with maximum recovery rate which can be used as an alternative to the stressful, costly, and laborious surgical approach.

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